Drug synthesis II
Tapio Nevalainen
2012

Synthesis of Prodrugs

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Drug Functional Groups and Synthesis of Prodrugs

Drug-X-R,

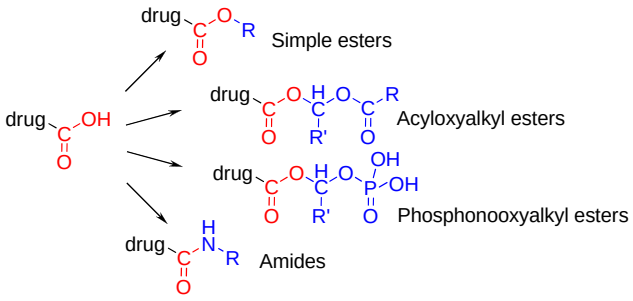
where X is the fuctional group in a drug, in which promoiety R can be attached.

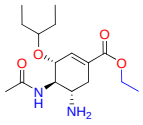
X can be NH, CO_2H, OH, SH, CONH, SO_2NH, C=O

Prodrug should be:

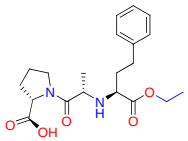
- inactive and nontoxic
- easily synthesizable
- chemically stable outside site of action
- bioreversible (parent drug must be regenerated in vivo)

Promoieties for carboxylic acids

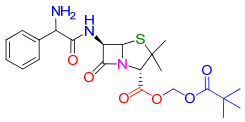




Oseltamivir (Tamiflu)



Enalapril



Pivampicillin

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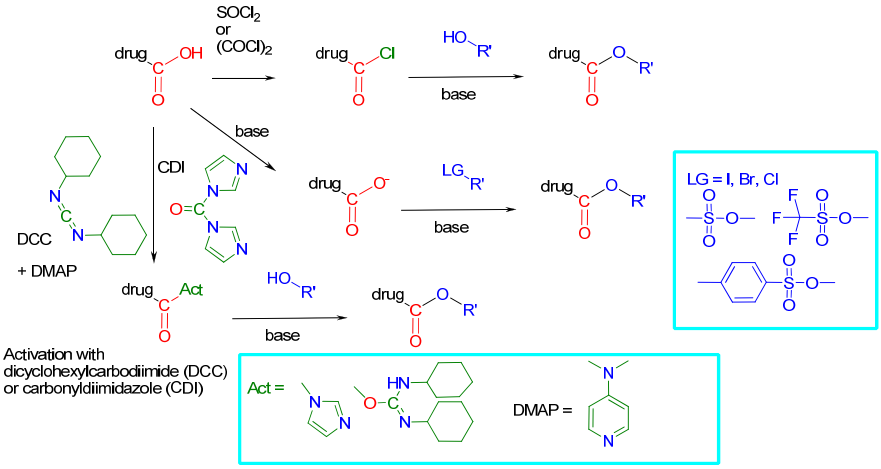
Synthesis of Esters



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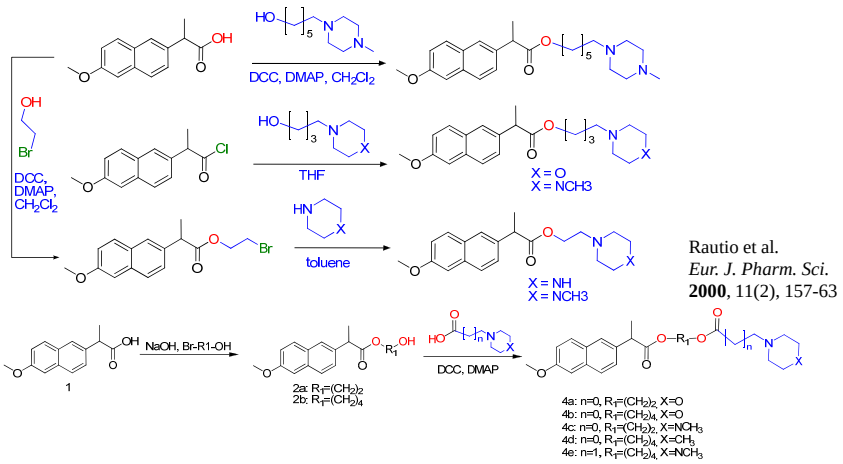
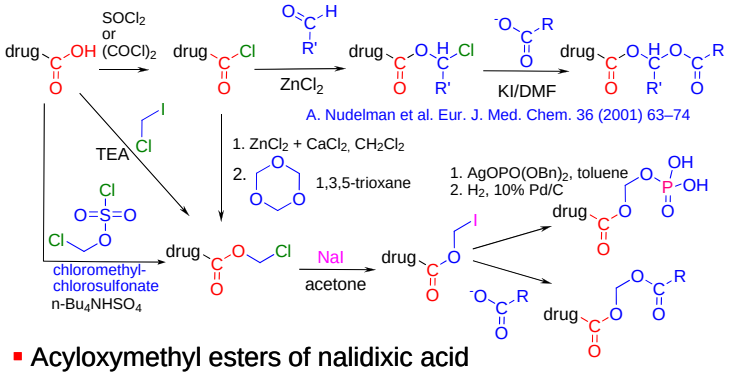
Synthesis of Naproxen Prodrugs for Topical Drug Delivery



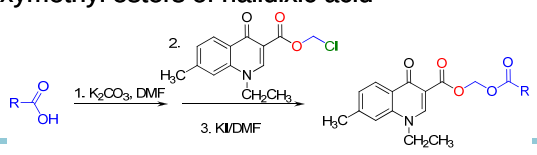
Rautio et al.
Eur. J. Pharm. Sci.
2000, 11(2), 157-63

Rautio et al. *J. Med. Chem.* **2000,** 43, 1489-1494

Synthesis of Acyloxyalkyl Esters



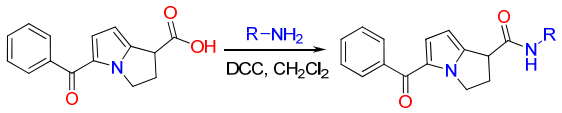
- Acyloxymethyl esters of nalidixic acid



Bioorganic & Medicinal Chemistry, 14 (8), 2006, 2569-2580

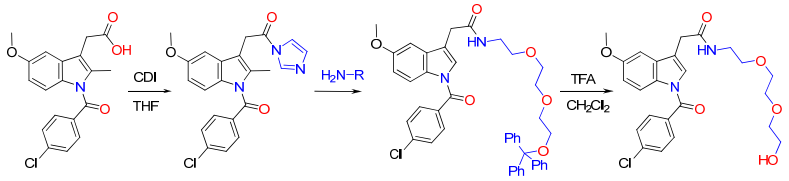
Synthesis of Amides

- Ketorolac amide prodrugs for transdermal delivery



Int. J. Pharm. 293 (2005) 193–202

- Indomethacin triethylene glycol amide prodrug



Bioorg. Med. Chem. Lett. 16 (2006) 1874–1879

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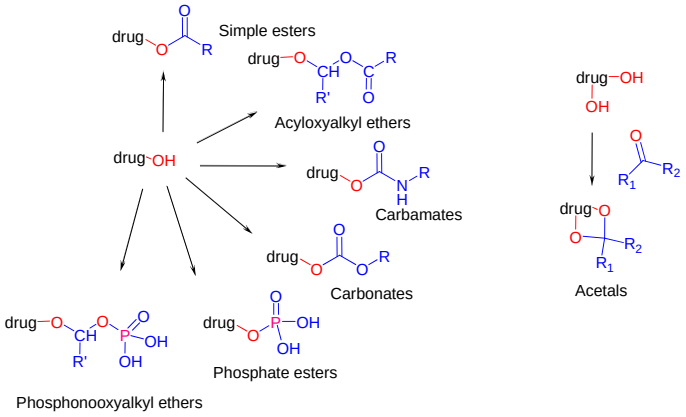
Promoieties for Hydroxyl Group



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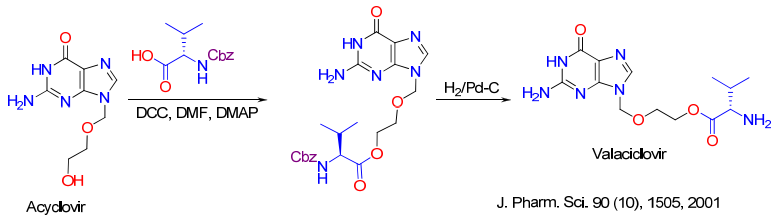
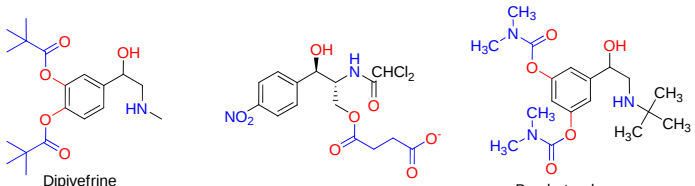
Promoieties for Hydroxyl Group



Acyclovir

Valaciclovir

J. Pharm. Sci. 90 (10), 1505, 2001



Dipivefrine
(prodrug of adrenaline)

Chloramphenicol succinate

Bambuterol
(prodrug of terbutaline)

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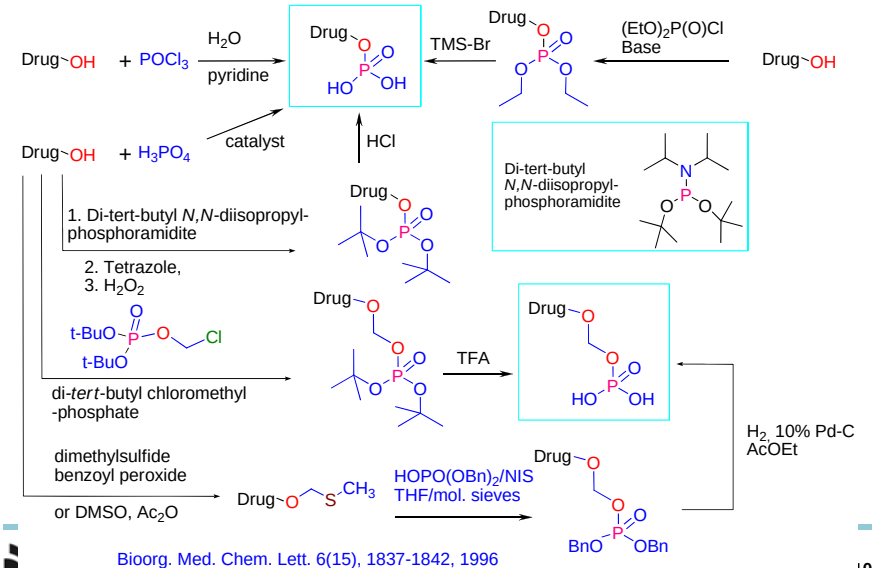
Synthesis of Phosphates

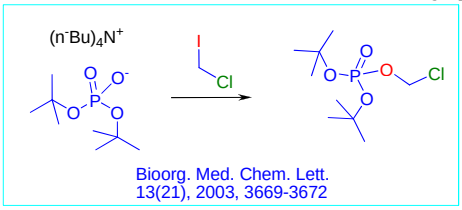


Bioorg. Med. Chem. Lett. 6(15), 1837-1842, 1996

10

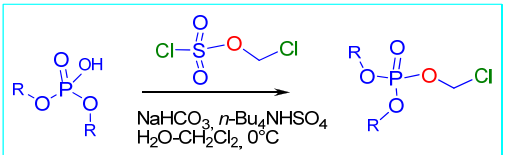
Preparation of Chloromethyl Phosphates

- **Chloromethyliodide with ammonium salt of di-tert-butyl phosphoric acid**



Bioorg. Med. Chem. Lett.
13(21), 2003, 3669-3672

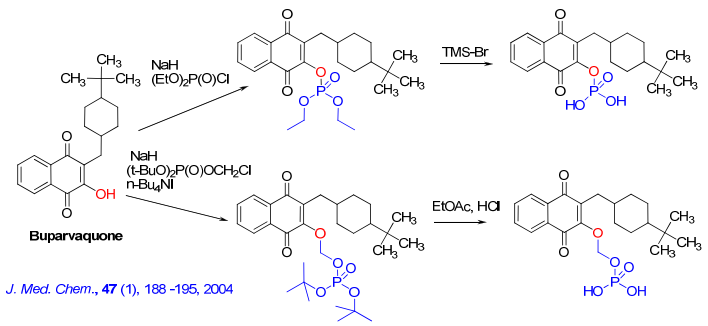
- **Chloromethyl chlorosulfate with dialkyl and or dibenzyl phosphates**



A. Mäntylä et al. Tetrahedron Lett.
43, 2003, 3793–3794

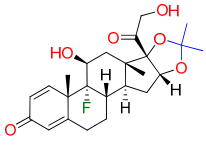
Selective Synthesis of Phosphate Monoesters from Phosphoric Acid

Buparvaquone phosphate prodrugs

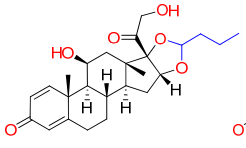


J. Med. Chem., **47** (1), 188 -195, 2004

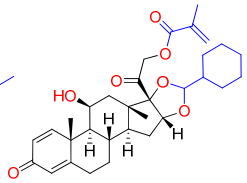
Acetonides and Acetals of Corticosteroids



Triamcinolone
(Nasacort)

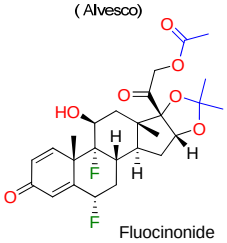


Budesonide
(Rhinocort, Pulmicort)



Ciclesonide
(Alvesco)

- Ciclesonide (CIC) is both prodrug and **softdrug**. It is activated by esterases in to active drug desisobutyryl-CIC
- Fluocinonide is a prodrug that allow dermal absorption by “masking” the hydroxyl groups (that can interact with the skin or binding sites in the keratin)



Fluocinonide
(Lidex)

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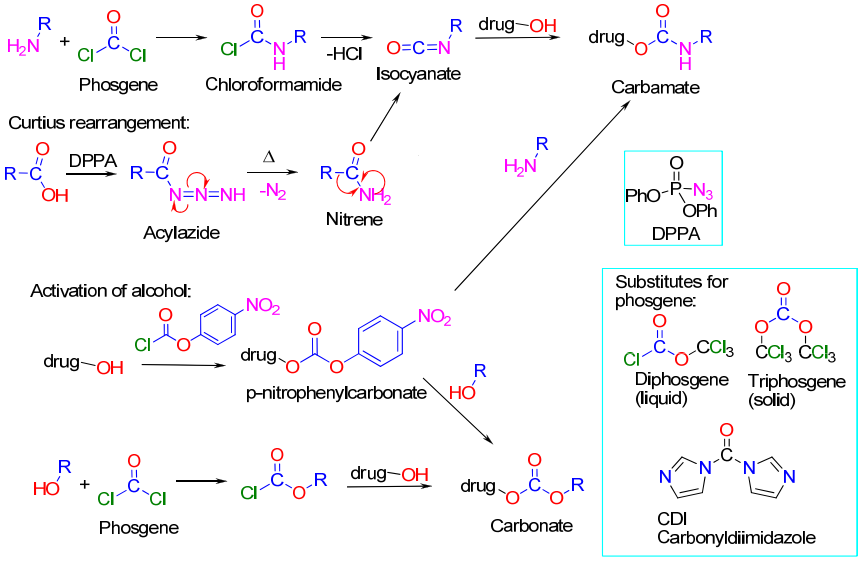
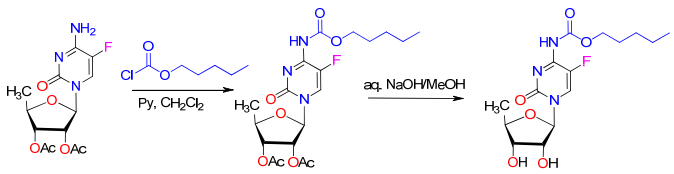
Synthesis of Carbamates and Carbonates

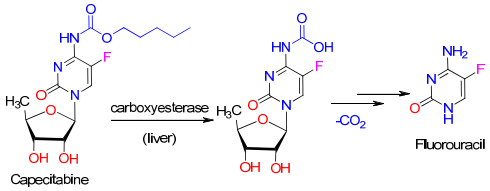


Synthesis of Capecitabine (Xeloda) a prodrug of antitumor agent 5-fluorouracil



Nuclear Medicine and Biology 31, (2004), 1033–1041

- Activation to the antitumor drug 5-fluorouracil



Biochemical Pharmacology 68, (2004), 2097–2106

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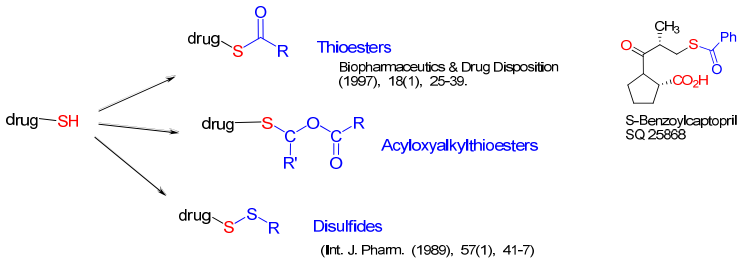
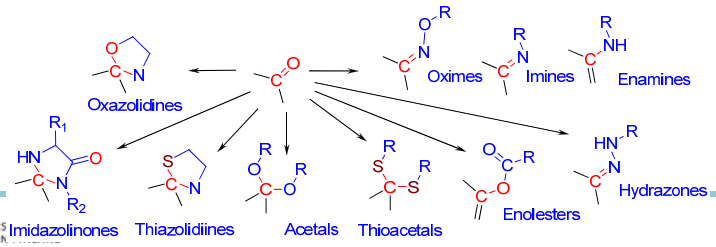
Promoieties for Thiols



Promoieties for Carbonylgroup



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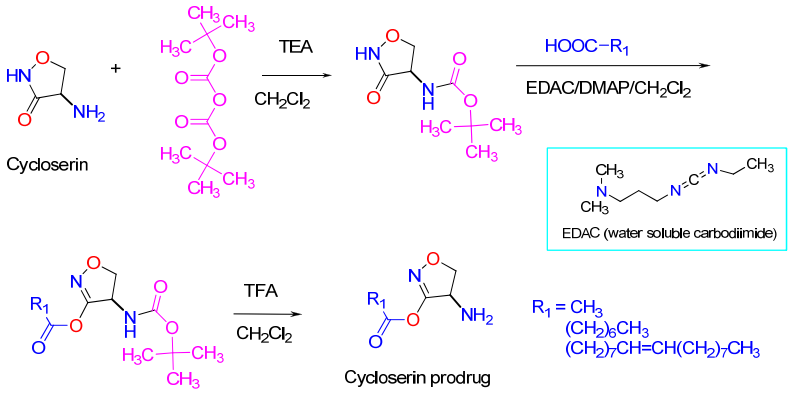
Example of Enolester: 4,5-dihydroisoxazol-3-yl

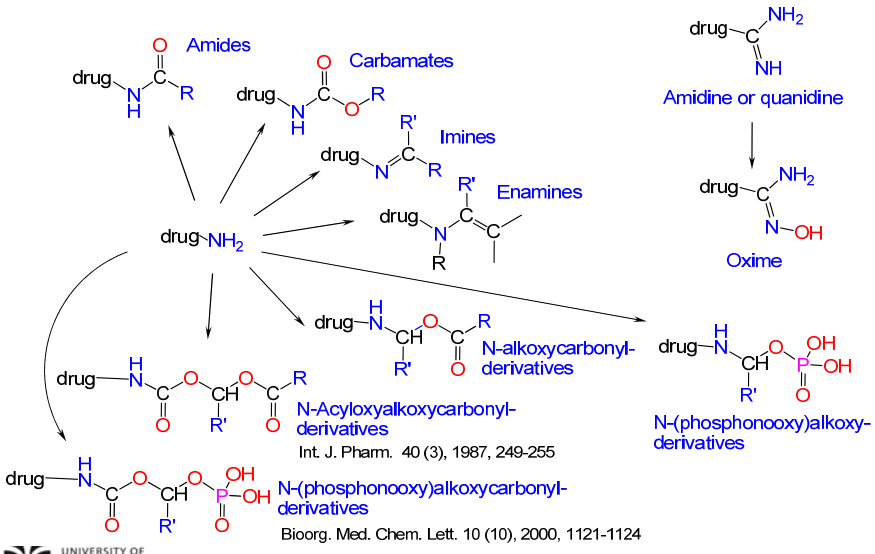
fatty acid esters to improve skin permeation of cycloserine



Cycloserine fatty acid derivatives as prodrugs: Synthesis, degradation and in vitro skin permeability, Chem. Pharm. Bull.50(4):554-7,2002

17

Promoieties for Aminogroup



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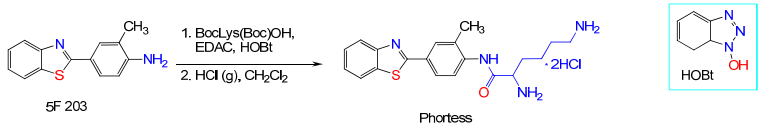
Promoieties for Amino Group

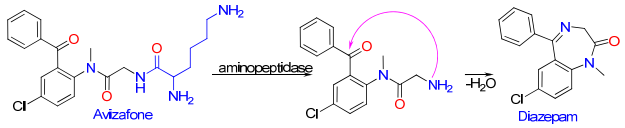
- Phortess, a water soluble pro-drug of the anti-cancer agent 5F 203

J. Med. Chem. 2002, 45, 744-747



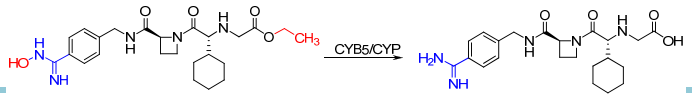
- Avizafone for diazepam avoids drowsy side effects of diazepam

J. Pharm, Pharmacol. 1990, 42(4), 247-51



- Ximelagatran, a prodrug form of direct thrombin inhibitor melagatran

Drug. Metab. Dispos. 2003, 31, 645-651



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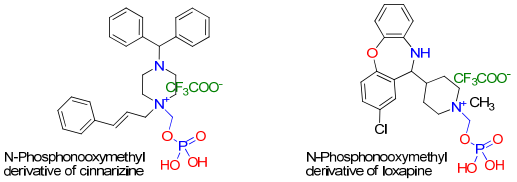
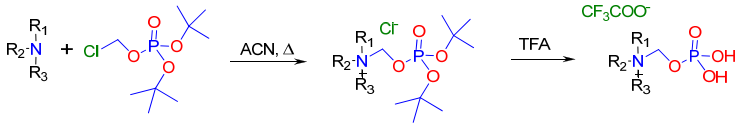
Prodrugs for tertiary amines

- *N*-Phosphonooxymethyl Prodrugs of Tertiary Amines



- General Synthetic Scheme



Krise et al. *J. Med. Chem.*, **42** (16), 3094 -3100, 1999

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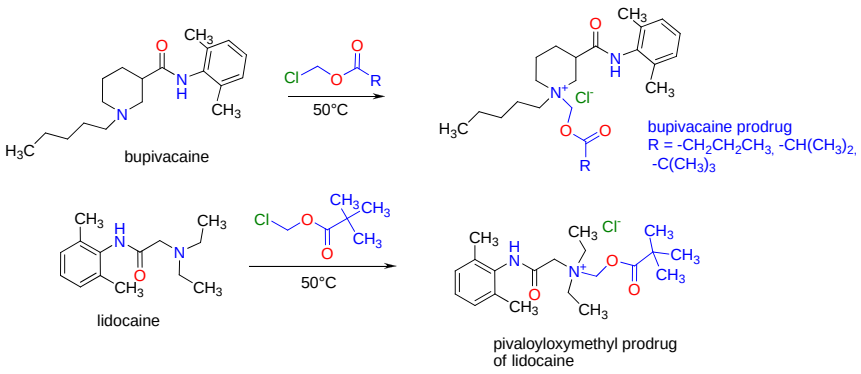
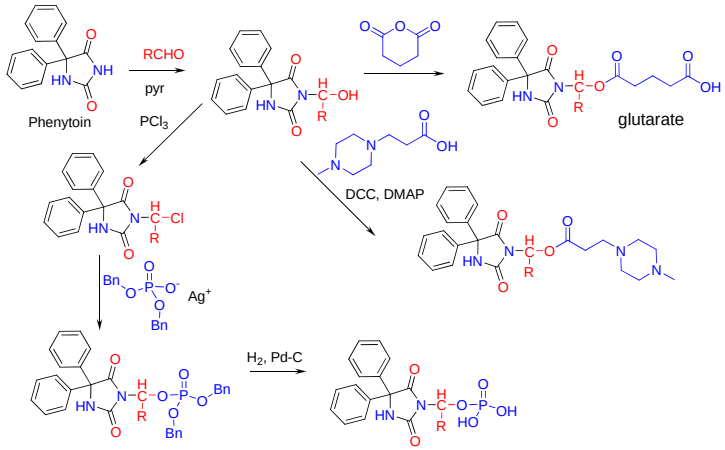
Prodrugs for tertiary amines

- *N*-acyloxymethyl prodrugs of bupivacaine and lidocaine
  (Eur. J. Pharm. Sci. 24 (5), 2005, 433-440)



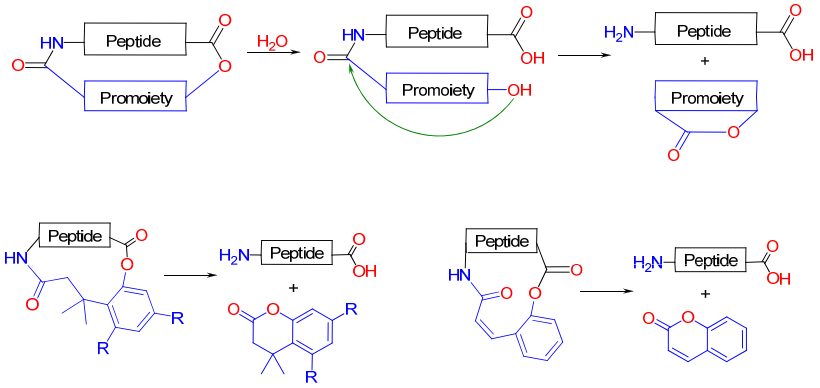
The synthesis of water-soluble phenytoin prodrugs



Bioorg. Med. Chem. Lett. 9 (1999) 1859-1862

Cyclic peptide prodrugs

- The two-step activation of peptide prodrugs



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Curr. Pharm. Des. 1999, 5(4):265-87

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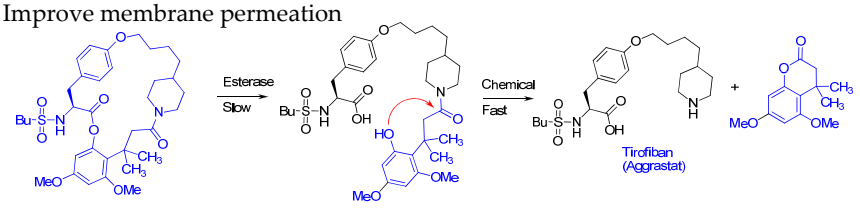
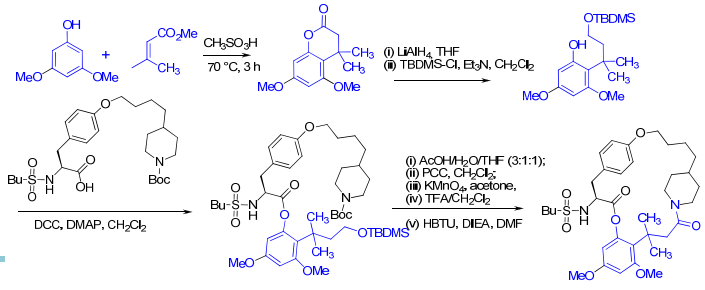
Cyclic Prodrug of Tirofiban

- Cyclic prodrug consisting of phenylpropionic acid linker between the piperidinylamine and the -COOH group
- Improve membrane permeation



- Synthesis



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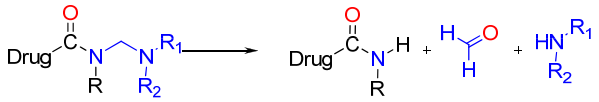
Org. Lett., **4** (4), 549 -552, 2002

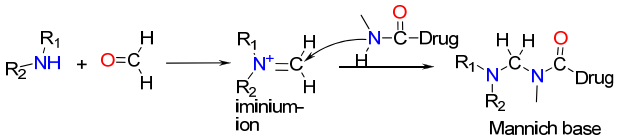
HBTU = O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate
DIEA = Diisopropylethylamine

Mannich bases as Prodrugs

- N-Mannich base prodrugs can be applied to both -NH acids (e.g. amides) and amines, and undergo bioconversion to release the parent -NH acid or amine and an aldehyde by chemical hydrolysis in aqueous, alkaline, and slightly acidic solutions.

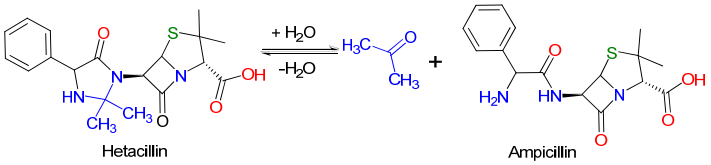


- Mannich reaction is nucleophilic addition reaction of an aldehyde and any primary or secondary amine to produce resonance stabilized schiff base (iminium ion). The addition of a carbanion from a CH acidic compound (enolizable carbonyl compound, amide, carbamate, hydantoin or urea) to the schiff base gives another base called the Mannich base.

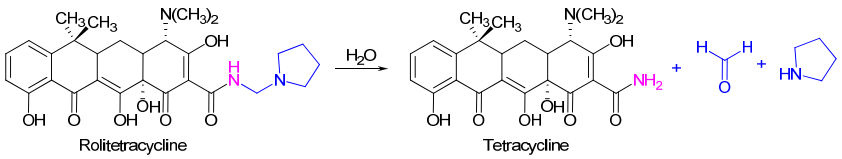


Mannich Base Prodrugs

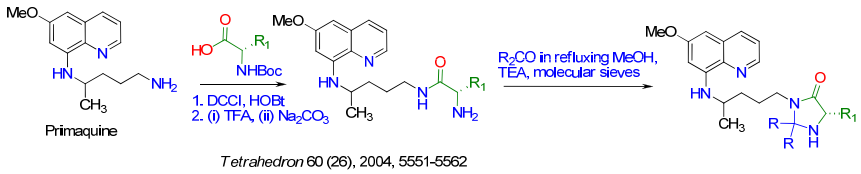
- Hetacillin is rapidly hydrolyzed to ampicillin in aqueous solutions and in vivo (U. Klixbull and H. Bundgaard, *Int. J. Pharm.* **23** (1985), pp. 163–173)



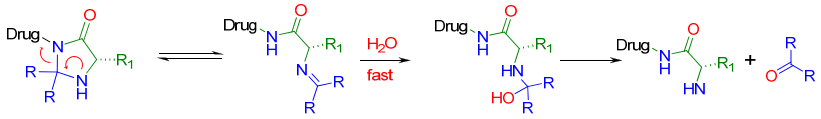
- Rolitetracycline liberates tetracycline in vivo



Imidazolidin-4-one Derivatives of Primaquine



- Mechanism of hydrolysis



Tetrahedron 62, (2006), 9883–9891

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